REMARKS

Applicants have carefully considered this Application in connection with the Examiner's Office Action, and respectfully requests reconsideration of this Application in view of the above amendments and the following remarks.

Claims 1-16, 25, 39, and 40 are withdrawn as being part of a non-elected invention, and Claims 17-24, 26-38 are under Examination.

Applicants have amended Claim 17-22, 23, 24, 32. and 26. These amended claims find support in the specification in paragraphs: [0044]-[0090], [0059], [0165]–[0173], Example 4, and the original claims.

I. Election/Restrictions

The Examiner has acknowledged Applicants' election of Group II, Claims 17-38, SEQ ID No: 1, and stimulating angiogenesis as the goal of the claimed treatment method in Applicants' response of February 2, 2006. However, the Examiner is of the opinion that the Applicants were not entirely responsive to the restriction requirement of 11/30/2005, in that one specific cell type was not elected from the group consisting of somatic cells, stem cells or germs cells, as recited in Claim 32. Therefore, the Examiner has modified the restriction requirement of November 30, 2005, to rejoin all cell types with the invention of Group II. Additionally, the Examiner has also withdrawn Claim 25 as being drawn to a non-elected invention because Applicants have Elected examination of SEQ ID NO: 1 and Claim 25 recites SEQ ID NO.: 2. The Examiner has stated that Claims 17-24, and 26-38 are under examination in the instant office action.

In response, Applicants have withdrawn Claim 25.

II. Objections to Claims:

The Examiner has required that the non-elected subject matter be deleted from Claim 17-24 and 26-38.

In response, Applicants have amended the claims to delete all non-elected subject matter from the instant claims.

III. Objections to Specification:

The Examiner is of the opinion that the term *"MyoD"* in paragraph [0162] with reference to Figure 6 is inconsistent with the title appearing on Figure 6 and the description in paragraph [0036].

In response, Applicants submit that the discussion comprises paragraphs [0162] – [0167] and Figures 6 and 8 pertain to both *"MyoD"* and *"myogenin."* Applicants submit that in paragraph [0162], the term *"MyoD"* was used instead of *"myogenin"* to describe the data in Figure 6. The Examiner has pointed out that this typographical error is inconsistent with other sections and Figures descriptions of the specification. Applicants have amended paragraph [0162] to correct the typographical error in connection with the term *"MyoD,"* see above. The correction of the term *"MyoD"* to "*myogenin*" is now consistent with the terms used in the figure title and the Figure 6 description in paragraph [0036]. Additionally, this correction does not constitute new subject matter because the title appearing on Figure 6 is consistent with this amendment.

IV. Claim Rejections 35 U.S.C. § 112, Enablement:

The Examiner has stated that Claim 17 does not reasonably provide enablement for one of ordinary skill in the art. The Examiner is of the opinion that Claim 17 refers to stimulating angiogenesis in ANY tissue, with ANY nucleic acid encoding ANY IGF-I.

The Examiner is further of the opinion that the breadth of Claims 17, 19, and 24 are not enabled. The Examiner has stated that Claim 17 recites, "a nucleic acid sequence encoding an IGF-I or functional biological equivalent thereof" and Claim 19 recite, "wherein the encoded IGF-I or functional biological equivalent has an amino acid sequence that is at least 85% identical to SEQ ID No: 4; and Claim 24 recites, "wherein a construct nucleic acid sequence is at least 90% identical to SEQ ID NO: 1."

Additionally, the Examiner has cited papers to indicate the teachings of IGF-I protein structure, function, and the mechanisms of IGF-I signaling through both insulin and IGF-I receptors. For example, the Examiner has stated on Page 8, second paragraph:

"It was well known at the time of the invention that IGF-I possesses cysteine residues that participate in disulfide bond formation and that said disulfide bond formation is important for proper protein folding and the resultant tertiary structure required for proper biological function," that was taught by Milner et al.

On Page 9, second paragraph, the Examiner further directed Applicants' attention to Claim 24, indicating that:

"Claim 24 reads on a nucleic acid construct wherein the entire IGF-I encoding nucleic acid fragment can be replaced with a nucleic acid of any nucleotide composition. For example SEQ ID No: 1 contains 5,423 nucleotides and a nucleic acid sequence that is 90% identical to SEQ ID No: 1 would tolerate replacement of up to approximately 542 nucleotides. The nucleotides sequence encoding IGF-I being approximately 461 nucleotides, Claim 24 reads on a nucleic acid construct that does not even encode IGF-I. The specification provides no guidance as to how an artesian would make or use the claimed invention."

In response, the Applicants have amended the claims in accordance to what was indicated to be enabling by the Examiner (See Page 4 of Office Action and amended claims above). Support for these amendments, it parts, was described in Example 4, including paragraphs [0150], [0165]-[0173]. Applicants further submit that one of ordinary skill in the art would understand that the claim language indicates that the nucleic acid sequence of the invention encodes IGF-I or functional biological equivalent thereof. If the practitioner needed further guidance, they would be drawn to paragraph [0059] in the specification to determine the definition of the term IGF-I or functional biological equivalent thereof, which states:

[0059] *The term "functional biological equivalent" of IGF-I as used herein is a polypeptide that has a distinct amino acid sequence from a wild type IGF-I polypeptide while simultaneously*

having similar or improved biological activity when compared to the IGF-I polypeptide. The functional biological equivalent may be naturally occurring or it may be modified by an individual. A skilled artisan recognizes that the similar or improved biological activity as used herein refers to facilitating and/or releasing IGF-I and stimulating angiogenesis. Methods known in the art to engineer such a sequence include site-directed mutagenesis.

Based on the combination of the Claim 17 limitation and the support from the specification described above, one of ordinary skill in the art would understand that a nucleic acid sequence that is 90% identical to SEQ ID NO: 1 should encode an IGF-1 amino acid having a specific biological activity. In contrast, a nucleic acid sequence that has 90% identity but does NOT encode IGF-1 or its functional biological equivalent, and does NOT contain a specific biological activity, would NOT read on the instant claims. However to clarify this point, Claims 17-21 have been amended to include structural limitations required for a biological activity capable of binding an IGF-I receptor. Support for each of these amendments can be found in the specification in paragraphs [0005], and [0044]-[0090], which describes specific terms that are utilized in the claims.

As such, Applicants respectfully submit the rejections of Claims 17, 19, and 24 are now moot.

V. Claim Rejections 35 U.S.C. § 112, Written Description:

The Examiner is of the opinion that Claims 17-24 and 27-38 do not comply with the written description requirement such that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors(s) had possession of the claimed invention. More specifically, the Examiner is of the opinion that "IGF-I or functional biological equivalent thereof" encompasses a large number of variants and molecules, but the specification only discloses one full length human IGF-I. As such, according to the Examiner, the specification does not describe the complete structure of a representative number of species for the large genus.

In response, Applicants have amended Claim 17 to include a structural limitation to a representative number of species for the large genus, namely, the IGF-I or functional biological

equivalent is capable of binding to an IGF-I receptor ("IGF-IR"). Support for this amendment can be found in paragraph [0005] of the specification. Additionally, Applicants submit that one of ordinary skill in the relevant art understands that an IGF-I or IGF-I derivative that are so structurally mutated that do not bind to the receptor, or do not fold correctly, or the tertiary structure is altered are excluded, they would not provide a similar or improved biological function. However, functional biological equivalents analogs that have structure features that allow the analog to bind the IGF-I receptor also have a similar function, as defined in the paragraphs [0005] and [0059].

The court expressly held: *"it is possible for a specification to enable the practice of an invention as broadly as it is claimed, and still not describe that invention." In re DiLeone*, 436 F.2d 1404, 1405, 168 U.S.P.Q. 592, 593 (C.C.P.A. 1971). As an example, the court posited the situation *"where the specification discusses only compound A and contains no broadening language of any kind. This might very will enable one skilled in the art to make and use compounds B and C; yet the class consisting of A, B, and C has not been described." Id.*

Applicants further submit that species-specific IGF-I were known in the art at the time of this invention (Fawcett and Bulfield, 1990; Inoue et al., 2003; Otte et al., 1996; Tanaka et al., 1998; Wang et al., 2003), see IDS filed. These references indicate significant homology between species. Applicants submit that a recitation of all those sequences or experimentation with many sequences already known in the art would have been unnecessary. Additionally, one of ordinary skill in the art at the time of the invention would have known that the IGF-I amino acid sequence is identical for humans, cows, dogs, horses and pigs (Nixon et al., 1999), even though the nucleic acid sequence may be modified slightly or different due to degeneracy of codons. Applicants submit that one or ordinary skill in the art could create a list of all degenerate variants of a nucleotide sequence for any encoded protein using sequencing programs that were available to the public at the time of the invention. Thus, the use of a construct encoding for human IGF-I or functional biological equivalents thereof, de facto enables many other species and derivatives of a genus without undue experimentation. Therefore, Applicants submit that human IGF-I that was used as a representative example can reasonably enable the broader genus. The amended claim adds the specific structural

feature of the IGF-I, or functional biological equivalent thereof, and its ability to bind a IGF-I receptor which distinguishes the claimed genus from other non-functioning members.

VI. Claim Rejections 35 U.S.C. § 112, second paragraph:

The Examiner is of the opinion that Claims 17-24, and 26-38 are indefinite. More specifically, the Examiner has held that the claims do not recite any positive steps that clearly relate back to the preamble. Additionally, the Examiner is of the opinion that Claims 17 and 23 contain contradictory recitations in connection with the terms "substantially free from a viral backbone: and "a viral vector."

In response, Applicants have amended Claim 17 to recite positive steps that clearly relate back to the preamble. For example,

> *"thereby delivering to the cells of the muscle tissue of the subject the isolated nucleic acid expression construct that enables an in vivo expression activity for the encoded IGF-I or functional biological equivalent thereof stimulating angiogenesis in the tissue of the subject."*

Additionally, the term *"a viral vector"* has been removed from Claim 23.

VII. Claim Rejections 35 U.S.C. § 102:

The Examiner is of the opinion that Claims 17, 19-23, and 31-38 are anticipated by Coleman et al, Journal of Biological Chemistry, 270, 12109-12116, 1995 ("Coleman '1995"). Coleman '1995, teaches a method of generating transgenic mice that exhibit muscle cell specific expression of IGF-I. The Examiner is of the opinion that the intended use limitations bear little weight on the determination of patentability. Thus, the Examiner has concluded that the method steps taught by Coleman '1995 are the same, and practice of the process would inherently result in the same outcome.

The plasmid construct taught by Coleman '1995 used to generate the transgenic mice comprises avian skeletal alpha-actin myogenic promoter region and the avian skeletal alpha actin

myogenic 3'UTR operably linked to the nucleic acid coding region of the human IGF-I. Coleman '1995 teaches that the transgenic mice exhibit muscle specific expression of human IGF-I, and, as such, the plasmid DNA construct taught by Coleman '1995 was delivered into the muscle tissue of the transgenic mice.

In response, Applicants have amended Claim 17 to replace the term "delivering" with the term "injecting." Additionally, Applicants submit that Coleman '1995 does not teach or describe the step of "injecting into a muscle tissue of the subject an isolated nucleic acid expression construct." The court has held:

> Anticipation requires identity of invention. The claimed invention, as described in appropriately construed claims, must be the same as that of the reference in order to anticipate. *Glaverbel Societe Anonyme v Northlake Marketing & Supply Inc.*, 33 U.S,P,.Q,2d 1446, 1498 (Fed. Cir. 1995).

Transgenic animals are produced by injecting a plasmid into the fertilized egg of the animal allowing the injected DNA to become incorporated into the genomic DNA, and implanting the modified egg into a foster mother for gestation. Due to the nature of transgenic animals, the transgenic plasmids are injected at such an early stage it is not possible to inject the plasmid of Coleman '1995 into a muscle tissue of the transgenic subject because the embryo does not even have muscle.

The Courts have held:

"Anticipation" under 35 U.S.C. 102(a) and (b) means that a single prior art reference identically shows every element of the claim being examined. *Orthokinetics, Inc. v Safety Travel Charis, Inc.*, 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (Fed. Cir 1986); *Akzp N.V. v United States Intl. Trad Commission* 808 F.2d 1471, 1 U.S.P.Q.2d 1241 (Fed Cir. 1986; *In re Bond*, 910 F.2d 831, 15 U.S.P.Q.2d (Fed Cir. 1990).

Applicants submit that the compositions of the Coleman '1995 are also substantially different from the present invention. For example, Coleman 1995 discloses a myogenic-specific vector for

the over-expression of IGF-I within muscle cells, utilizing the skeletal α-actin promoter (*See*, Abstract). Coleman '1995 describes characteristics of TRANSGENIC animals that over-express specifically in all muscles using a transgene that comprises a large piece of the skeletal alpha actin promoter (733 base pairs), a human IGF-I cDNA, and a 3'UTR of skeletal alpha actin. Despite this large amount of overexpression, Coleman '1995 does NOT find any effects on angiogenesis, suggesting that the method steps taught by Coleman '1995 and the method steps in the instant invention are NOT the same.

The Examiner has also stated that Coleman '1995 does NOT teach a myogenic promoter comprising a nucleic acid sequence that is at least 85% identical to SEQ ID No:3; does NOT teach a nucleic acid construct comprising the nucleotide sequence of SEQ ID NO.: 1; and does NOT teach transfection enhancing techniques/compounds such as electroporation or transfection facilitating polypeptides as a means to deliver nucleic acids to cells. Applicants submit differences in teachings stated by the Examiner are manifest in the difference in the results and can be illustrated in practice because the process of Coleman '1995 does NOT inherently result in the same outcome as the instant invention.

The courts have held:

Where the allegedly prior art reference is lacking an element of the examined claim or where there are differences between the reference disclosure and such claim then anticipation is negated and a rejection of the claim is only possible under obviousness. *Atlas Powder Co. v E.I. Du Pont de Nemours and Co.*, 224 U.S.P.Q. 409 (Fed Cir. 1984); *Titanium Metals Corp. V Banner* 227 U.S.P.Q. 773 (Fed Cir. 1985);

Therefore, Applicants submit Coleman '1995 does NOT teach or suggest a method for stimulating angiogenesis in a subject, comprising: injecting into a muscle tissue of the subject an isolated nucleic acid expression construct. Because the element of "injecting into a muscle" is missing from Coleman '1995, the article cannot be a 35 U.S.C. § 102 reference in connection with the amended claims. At best, Coleman '1995 may be viewed as a § 103 reference, however, the nature of methods used to produce transgenic animals is so vastly different and the elements taught

are so dissimilar, Applicants submit the Coleman '1995 reference does not even qualify as a 35 U.S.C. §103 reference (See Next Section).

VIII. Claim Rejections 35 U.S.C. § 103:

The Examiner has rejected Claims 17-24, and 26-38 as being unpatentable over Coleman '1995, in view of Draghia-Akli, Nature Biotechnology, 17:1179-1183, 1999 ("Draghia-Akli '1999"); Fewell et al., Molecular Therapy, 3:574-583, 2001 ("Fewell '2001); and Isner, U.S. Patent 6,121,246 ("the '246 Patent").

The Examiner is of the opinion that Coleman '1995 the teachings of Coleman '1995 showed how the practice of the process of producing transgenic animals would inherently result in the same outcome as the instant invention (See Above). However, the Examiner has stated that Coleman '1995 does NOT teach several elements associated with the current application, namely a myogenic promoter comprising a nucleic acid sequence that is at least 85% identical to SEQ ID No: 3; does NOT teach a nucleic acid construct comprising the nucleotide sequence of SEQ ID NO.: 1; and does NOT teach transfection enhancing techniques/compounds such as electroporation or transfection facilitating polypeptides as a means to deliver nucleic acids to cells.

The Examiner is of the opinion that Draghia-Akli '1999 teaches a myogenic promoter consisting of the nucleic acid of SEQ ID No: 3 (i.e. SPC5-12) operably linked to a nucleic acid encoding human growth hormone releasing hormone ("GHRH"). The Examiner has also indicated that Draghia-Akli teaches intramuscular injection of the plasmid construct into pigs and then electroporating the injected muscle of the pig to more efficiently deliver the plasmid to the muscle cells.

The Examiner is of the opinion that the '246 Patent teaches intramuscular injection of plasmid DNA complexed with a charged polypeptide poly-L-glutamate into mice followed by electroporation resulting in more efficient transfection of the cells within the injected muscle.

The Examiner is of the opinion that it would have been obvious to modify the method of Coleman '1995 with a reasonable expectation of success by: (1) interchanging the avian skeletal

alpha-actin myogenic promoter with the strong muscle-specific synthetic SPc512 promoter taught by Draghia-Akli'1999; (2) complexing plasmid DNA with poly-L-glutamate prior to intramuscular injection of said plasmid DNA as taught by Fewell '2001 and (3) subjecting muscle tissue injected with said plasmid DNA to electroporation as taught by both Draghia-Akli and Fewell '2001 with a reasonable expectation of success.

The Examiner is also of the opinion that intended use limitations bear little weight on determination of patentability. The limitation for "a method for stimulating angiogenesis" does not carry patentable weight in the determination of anticipation for the claimed products. This is because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art. In a claim drawn to a process, the intended use must result in a manipulative differences as compared to the prior art.

In response, Applicants have amended Claim 17 to recite positive limitations that relate back to the preamble, as such, "stimulating angiogenesis" is a non-preamble limitation that was not taught or suggested by any of the cited references. Applicants submit that Claim 17, as amended, contains a limitation for "stimulating angiogenesis" that DOES carry patentable weight in the determination of anticipation for the claimed products.

Additionally, Applicants submit that both structural differences and manipulative differences exist between the instant application and the Coleman '1999 reference. For example, the Examiner has already stated that there are structural differences in the promoter, and expressed genes between the Colemann '1999 and the Applicants claims. Applicants submit, as described in the previous section, amended Claim 17 contains a manipulative step of "injecting into a muscle tissue of the subject an isolated nucleic acid expression construct," which is not possible with Coleman '1999 because of the nature of transgenic animals (as discussed in previous section). Applicants submit that the Coleman '1999 should NOT be used as a §103 reference.

In discussing a rejection under 35 U.S.C. 103, the Court, in *In re Wesslau*, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965) held that:

> It is impermissible within the framework of Section 103 to pick and **choose** from any one reference only so much of its as will support a given position, to the **exclusion** of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. [Emphasis added].

The Examiner cannot selectively abstract only certain parts of a particular reference and arbitrarily discard the remaining parts of the reference in order to support the Examiner's position, thereby using the Applicants' claimed subject matter as a blueprint by which the prior art is constructed. This type of piecemeal reconstruction of the references in light of Applicants' disclosure cannot be the basis for holding the invention obvious. *In re Kamm and Young*, 172 U.S.P.Q. 298, 301-302 (C.C.P.A. 1972).

The Examiner has concluded that the method steps taught by Coleman '1995 are the same, and practice of the process would inherently result in the same outcome. However, the consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have reasonable likelihood of success, viewed in the light of the prior art. **Both** the suggestion and the expectation of success must be founded in the prior art, not the Applicants' disclosure. Thus, "obvious-to-try", or "obvious-to-test" or "experiment" is not a proper standard of 35 U.S.C. 103. *In re Goodwin*, 198 U.S.P.Q. 1,3 (C.C.P.A. 1978); *In re Antonie*, 195 U.S.P.Q. 6,8 (C.C.P.A. 1977); *In re Geiger*, 2 U.S.P.Q. 2d 1276, 1278 (Fed. Cir. 1987); *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1532 (Fed. Cir 1988). In fact, the mere need for experimentation to determine parameters needed to make an invention work is an application of the often rejected "obvious-to-try" standard and falls short of the statutory obviousness of 35 U.S.C. 103. The inability of an expert to predict that results obtainable with a claimed product suggests non-obviousness, not routine experimentation. *Uniroyal Inc. v. Rudkin-Wiely Corp.*, 5 U.S.P.Q. 2d 1434, 1440 (Fed. Cir. 1988).

Applicants submit that the field of injecting expression vectors into the nuclei of fertilized mammalian eggs to produce transgenic animals and the field of tissue electroporation in full grown animals are not at the point were techniques used in either field are interconvertable. Applicants submit, one with ordinary skill in the art could not have used the three cited references to produce the instant invention, as amended. More specifically, the compositions and manipulations steps used to produce transgenic animals from a single fertilized egg are not obvious to be extrapolated to predictable results having manipulative steps of injecting a multi-billion cell muscle tissue for "stimulating angiogenesis," in a subject.

The following questions will illustrate that the Examiner has impermissibly used hindsight to selectively choose and pick "from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." See *In re Wesslan*, 147 U.S.P.Q 391, 393 (C.C.P.A. 1965).

WHERE ARE THE TEACHING OR SUGGESTION OF:

(a) **Selecting** only the disclosure from Coleman '1995 of delivering a plasmid construct encoding IGF-I in mice, but **discarding** the information that delivering the plasmid was done via transgenic technology that begins with a fertilized egg and not an intact animal?

(b) **Selecting** only the disclosure from Draghia-Akli '1999 of delivering plasmid vectors to the muscle by electroporation, but **discarding** the disclosure that the vectors were GHRH expression vectors that are structurally and functionally very different from IGF-I from the instant invention?

(c) **Selecting** only the disclosure from Fewell '2001 of delivering plasmid vectors to the muscle by electroporation in combination with poly-L-glutamate (at a different concentration and molecular weight compared to the instant invention), but **discarding** the disclosure that the vectors were Factor IX and erythropoietin

expression vectors and structurally and functionally very different from IGF-I of the instant invention?

More importantly, **NONE** of the referenced articles taught, suggested, or even mentioned the use of plasmids encoding IGF-I could be used for "simulating angiogenesis" in an animal. The teaching or suggestion to make the claimed combination and the reasonable expectation of success **must both be found in the prior art, not** in the Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). The key words here are "both must be found in the prior art." **Thus Applicants submit that NONE of the references listed above, either alone or in combination, suggest a reasonable expectation of success that an expression plasmid encoding IGF-I could be effectively delivered to a muscle tissue for stimulating angiogenesis in a subject in a subject.**

The Examiner is also of the opinion that SEQ ID No:1 of the instant invention is a hybrid plasmid consisting of fragments of the plasmids taught by Coleman '1995 and Draghia-Akli '1999. Applicants submit that Claim 17, as amended, is a method claim for "for stimulating angiogenesis" and not a composition claim. Even if the two sequences were identical, which they are clearly not, the use of IGF-I or functional biological equivalents thereof "for stimulating angiogenesis" was not taught, described, or suggested in any of the cited references.

IV. Conclusion

Applicants respectfully submit that, in light of the foregoing comments and amendments, all pending claims are now in condition for allowance. A Notice of Allowance is therefore requested.

If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,

T. G Chwang

T. Ling Chwang
Registration No. 33,590
JACKSON WALKER L.L.P.
901 Main Street, Suite 6000
Dallas, Texas 75202
Tel: (214) 953-5959
Fax: (214) 661-6870

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